

**II. REMARKS**

**A. Status of the Claims**

Claims 1, 3, 5, 7, 8, 10-12, 14, 18-19, 36-37, 39-40, 43-44, 52-53, and 56 are currently pending. Claims 2, 4, 6, 17, 21-35, 42, 45-51 and 55 were previously cancelled. Claims 13, 16, 20, 38, 41 and 54 have been cancelled herein without prejudice. Claim 1 has been amended without prejudice. It is respectfully submitted that no new matter has been added by virtue of this amendment.

**B. Double Patenting Rejection**

Claims 1, 3, 5, 7, 8, 11-16, 18-20 and 54 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3-16 and 18-20 of U.S. Patent No. 6,475,494.

In response, filed herewith is a terminal disclaimer over U.S. Patent No. 6,475,494, in compliance with 37 C.F.R. 1.321(c).

Applicants note that the obviation of an obvious-type double patenting rejection by the filing of a terminal disclaimer is not an admission, acquiescence, or estoppel on the merits of an issue of obviousness. *See Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870, 873-74, 20 U.S.P.Q.2d 1392, 1394-95 (Fed. Cir. 1991).

**C. Claim Rejections Under 35 U.S.C. § 103**

**1. Rejections over Crain 1 in view of Crain 2**

Claims 1, 8, 10, 11, 13, 18, 20, 36-41, 43 and 565 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. 5,580,876 to Crain et al. (Crain 1), in view of U.S. 5,512,578 to Crain et al. (Crain 2). The Examiner stated that "Crain 1 does not expressly teach the weight ratio of the opioid agonist and antagonist" and further stated that "Crain 2 teaches orally administering combination of opioid agonist and antagonist in a weight ratio of about 0.01 to about 1 of opioid antagonist to opioid agonist" and that "it would

have been obvious ... to prepare an oral dosage form of Crain 1 using the weight ratio ... in view of the teaching of Crain 2."

This rejection is traversed. Applicants respectfully submit that the presently claimed ratios are not encompassed by the weight ratios described by combining these references. Applicants respectfully direct the Examiner's attention to column 6, lines 60-65 of Crain 2, which states that "the dose of excitatory opioid receptor antagonist to be administered is 100 – 1000 times less than the dose of bimodally-acting opioid agonist to be administered, for example, about 1 microgram of said antagonist together with 100 – 1000 micrograms of said agonist." (Emphasis added). In other words, Crain 2 describes that the ratio of antagonist to agonist would be from .01:1 to .001: 1 which is different than the claimed ratios as set forth in Table 1 below:

TABLE 1

Claimed Combination	Claimed Ratio	Comparison to Crain 2 Ratio
naltrexone : hydrocodone	about 0.03:1 to about 0.27:1	lower value of claimed range is <u>300%</u> of the <u>higher</u> than upper value of Crain 2 range
naltrexone:oxycodone	about 0.037:1 to about 0.296:1	lower value of claimed range is <u>370%</u> of the <u>higher</u> than upper value of Crain 2 range
naltrexone:hydromorphone	about 0.148:1 to about 1.185:1	lower value of claimed range is <u>1,480%</u> of the <u>higher</u> than upper value of Crain 2 range
naltrexone:levorphanol	about 0.278:1 to about 2.222:1	lower value of claimed range is <u>2,780%</u> of the <u>higher</u> than upper value of Crain 2 range
naltrexone:morphine	about 0.018:1 to about 0.148:1	lower value of claimed range is <u>180%</u> of the <u>higher</u> than upper value of Crain 2 range

Applicants respectfully submit that a formulation prepared by one skilled in the art based on a combination of Crain 1 and Crain 2 would have a ratio of opioid agonist to antagonist of from .01:1 to .001:1. In contrast, based on the information presented in Table 1 above, the presently claimed ratios are from 180% to 2,780% of higher than the .01 to 1 ratio of the combination of Crain 1 and Crain 2. Accordingly, a combination of Crain 1 and Crain 2 fails to teach or suggest the weight ratios of the opioid agonist to opioid antagonist as recited in the present claims

Therefore, it is respectfully requested that the rejection under 35 U.S.C. §103(a) over Crain 1 in view of Crain 2 be removed.

## **2. Rejections over Crain 1 in view of Crain 2 and Kreek**

In the Office Action, claims 3, 5, 12, 14, 16, 19, 44, 52 and 54 were rejected under 35 U.S.C. § 103 (a) as being unpatentable over Crain 1 in view of Crain 2 and U.S. 4,769,372 to Kreek. The Examiner stated that Crain 1 and 2 "do not teach hydrocodone, oxycodone, hydromorphone, and meperidine" but Kreek teaches "hydrocodone, oxycodone, codeine, hydromorphone, meperidine, methadone, and morphine"

This rejection is traversed. As discussed above, Applicants respectfully submit that a combination of Crain 1 and Crain 2 fails to teach or suggest the weight ratios of the opioid agonist to opioid antagonist as recited in the present claims.

Applicants further submit that Kreek fails to cure this deficiency of the combination of Crain 1 and Crain 2, as Kreek fails to teach or suggest an opioid agonist/antagonist combination which contains naltrexone, let alone the specific combinations of opioid agonists with naltrexone in the specific weight ratios as recited in the present claims.

Therefore, Applicants respectfully request that the rejection under 35 U.S.C. §103 (a) over Crain 1 in view of Crain 2 and Kreek be removed.

**3. Rejections over Crain 1 in view of Crain 2 and Mitch et al.**

In the Office Action, claims 7, 15 and 53 were rejected under 35 U.S.C. §103(a) as being unpatentable over Crain 1 in view of Crain 2 and U.S. 5,998,434 to Mitch et al.

This rejection is traversed. As discussed above, Applicants respectfully submit that a combination of Crain 1 and Crain 2 fails to teach or suggest the weight ratios of the opioid agonist to opioid antagonist as recited in the present claims.

Applicants further submit that Mitch fails to cure this deficiency of the combination of Crain 1 and Crain 2 as this reference also fails to teach or suggest an opioid agonist/antagonist combination which contains naltrexone, let alone the specific combinations of opioid agonists with naltrexone in the specific weight ratios as recited in the present claims.

Therefore, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) over Crain 1 in view of Crain 2 and Mitch be removed.

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Reply to Office Action dated March 30, 2006

**III. CONCLUSION**

It is now believed that the above-referenced rejections have been obviated and it is respectfully requested that the rejections be withdrawn.

An early and favorable action on the merits is earnestly solicited. The Examiner is invited to contact the undersigned at the telephone number provided below if he believes that a telephonic interview will advance the prosecution of this application.

Respectfully submitted,

DAVIDSON, DAVIDSON & KAPPEL, LLC

By: \_\_\_\_\_

  
Robert J Paradiso  
Reg. No. 41,240

DAVIDSON, DAVIDSON & KAPPEL, LLC  
Patents, Trademarks and Copyrights  
485 Seventh Avenue, 14<sup>th</sup> Floor  
New York, New York 10018  
(212) 736-1940